UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington, D.C. 20231

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 14

Mailed
4/05/95
Gp. 1800

Serial Number: 08/026,957
Filing Date: March 5, 1993
Appellant(s): Petra Boyle et al.

James A. Giblin
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed November 3, 1994.

(1) Status of Claims.

The statement of the status of claims contained in the brief is correct.

(2) Status of Amendments After Final.

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(3) Summary of Invention.

The summary of invention contained in the brief is correct.

(4) Issues.

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

Issue #2: The rejection under 35 U.S.C. § 101 is withdrawn.

Issue #3: The objection to the specification and rejection of claims 1-14 under 35 U.S.C. § 101 is withdrawn. The specification remains objected to and claims 1-14 remain rejected under 35 U.S.C. § 112, first paragraph, rather than under 35 U.S.C. § 112, second paragraph, as indicated in Appellant's Brief On Appeal.

Issue #5: The objection to the specification and rejection of claims 1-14 under 35 U.S.C. § 112, first paragraph, with respect to the failure to provide a chain of custody for deposited cell lines is withdrawn in view of Appellant's arguments.

(5) Grouping of Claims.

The brief includes a statement that claims 1-14 do not stand or fall together but fails to present reasons in support thereof. Therefore, these claims are presumed to stand or fall together. Appellants request that the claims be considered separately for the reasons set forth in the body of the Brief. However, the Brief does not set forth any specific arguments to support a separate treatment of individual claims. Further, Appellant has failed to treat the claims separately during prosecution of the instant application. For the above reasons, claims 1-14 should stand or fall together.

(6) Claims Appealed.

The copy of the appealed claims contained in the Appendix to the brief is correct.

(7) Prior Art of Record.

No prior art are relied upon by the examiner in the rejection of claims under appeal.

(8) New Prior Art.

New references have been applied in a new ground of rejection in this Examiner's Answer and listed below:

R3. Seaver, S. S., "Monoclonal Antibodies In Industry: More Difficult Than Originally Thought," Genetic Engineering News 14(14):10, August 1994.

S3. Rhein, R., "Another Sepsis Drug Down--Immunex' TNF Receptor," Biotechnology Newswatch, October 4, 1993, page 1.

T3. Natanson et al., "Selected Treatment Strategies For Septic Shock Based On Proposed Mechanisms Of Pathogenesis," Annals Int. Med. 120(9):771-783, 1 May 1994.

U3. Hill, C. R., "Immunoaffinity Purification With Monoclonal Antibodies," in Monoclonal Antibodies: Principles and Applications, Birch et al., Eds., John Wiley & Sons, 1995, pages 121-136.

(9) Grounds of Rejection.

The following ground(s) of rejection are applicable to the appealed claims.

Claims 1-14 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-14 of copending application Serial No. 08/145,060. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Appellant has acknowledged that Continuation-In-Part application 08/145,060 does indeed contain the same claims (see Brief, Page 3, fourth full paragraph). Further, Appellant has not responded to the rejection other than to 1) request postponement of consideration of the provisional rejection, and 2) to indicate that "Applicants would, if necessary, file a Terminal Disclaimer to address any double patenting issue" (see Brief, page 4, fourth full paragraph). This is not persuasive. The provisional rejection is made under 35 U.S.C. § 101 since the claims are the same and Appellant has failed to take any appropriate action to rectify the double patenting issue. Further, a Terminal Disclaimer is not an appropriate remedy for statutory double patenting. Thus, claims 1-14 remain provisionally rejected under 35 U.S.C. § 101 for the reasons of record. In view of the above reasons, it is respectfully requested that the rejection

be affirmed.

The specification remains objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. This objection to the specification as lacking enablement and the subsequent rejection of claims 1-14 has two parts. First, Appellant has failed to teach one of ordinary skill in the art how to use the claimed invention and Appellant's alleged uses set forth in evidence and arguments filed after the filing date would not be readily apparent to one of ordinary skill in the art from the teachings of the specification. Second, Appellant has failed to enable the scope of the claims. These objections will be treated in order.

Appellant has not taught a specific use in the specification for the human anti-TNF antibodies of the claimed invention thus failing to enable one skilled in the art to use the claimed invention without undue experimentation. A careful reading of Appellant's specification has not revealed any statements or teachings setting forth the utility of the claimed invention. At best, one might infer that Appellants intend the claimed antibodies to be employed as therapeutic agents since Appellant states that "we are unaware of the disclosure of any monoclonal human antibodies specifically binding to TNFα even though such antibodies may have **a significant clinical value**" (see specification, page 3, first paragraph). As stated by the court:

> **But surely Congress intended § 112 to pre-suppose *full satisfaction* of the requirements of § 101. Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention.**

In re Kirk and Petrow, 153 USPQ 49, 53 (CCPA 1967). While

Appellant has discussed at some length the characteristics of the claimed B5 antibody, Appellant does not appear to have disclosed any intended uses for the claimed invention. Appellant has previously argued that "one skilled in the art would readily recognize the value of any monoclonal antibody directed to a specific substance such as TNF" (see Paper No. 3, page 4, first paragraph). Appellant further argues that "In the instant Application, the Applicants have not only stated that the antibodies have biological activity, they have indicated in the embodiments several specific uses of the antibodies. The antibodies have been found to be useful in Western Blot Assays, ELISAs, and FACS staining to name just a few" (see Brief, page 5, second full paragraph). Appellant further argues that "It should be noted that in a vigorous and separately argued written dissent in Kirk and Petrow by Judge G. Rich, 153 USPQ 266 at 273, the requirement of mentioning a specific use was applicable (only)...'at least in the absence of evidence that a specific use would be obvious'" and that "It is well known to those skilled in the art of monoclonal antibodies that any monoclonal antibody can be used to bind to a given substance. These uses may have many forms such as in diagnostic uses, purification, therapeutic uses, etc." (see Brief, page 5, third full paragraph). Appellant further argues that they have sufficiently taught the use of the claimed invention stating "it is the Applicant's position that they have done this in their specification as filed" and that "in support of this position, the Applicants enclosed a Declaration under 37 C.F.R. 1.132 by Professor Matthias Wabl, a person skilled in the art, pointing out that specific uses of the human anti-TNFα antibodies would be obvious." Appellant argues that the Wabl declaration states that "any monoclonal antibody, once generated, can be used in a variety of immunoassays which would be inherently useful for not only research but as diagnostic tools." (see Brief, paragraph bridging pages 5-6). Finally, Appellant argues that an Abstract

attached to the Wabl declaration shows "a trend toward efficacy in using murine anti-TNF to treat such patients" (see Brief, page 6, first full paragraph). These arguments are not persuasive for the reasons set forth *infra*.

While Appellant does disclose the binding of the claimed monoclonal antibodies in Western blots and other in vitro assays in the specification, such uses are purely for the purpose of characterizing the monoclonal antibodies and do not appear to have any correlation to diagnostic utilities. As evidenced by Seaver (R3) developing a monoclonal antibody suitable for diagnostics is not a trivial issue as Appellant would suggest and as stated by Wabl. Indeed, contrary to the assertions of Wabl, Seaver indicates that "Despite the apparent success of mabs in diagnostics, good antibodies are hard to find" and that "Selection of the final antibodies requires work with real clinical specimens" citing an example of the problems of using mabs in an ELISA (see paragraph bridging columns 3-4 and column 4, paragraphs 1-3). Seaver further indicates that "monoclonal antibodies have not been uniform success stories as diagnostic reagents. There are few good mabs for carbohydrates antigens. It has been difficult to find monoclonals for most cancers and infectious diseases...Tens of thousands of positive clones for infectious diseases such as chlamydia or for most cancers have been collectively screened, yet few, if any tests have reached the market" (see column 4, third full paragraph, emphasis added). Thus Seaver directly contradicts Appellant's assertion that the use of the claimed monoclonal antibodies in diagnostics would have been obvious to one skilled in the art.

Further, the declaration of Wabl is not sufficient to overcome the evidence. Wabl's assertions that "any monoclonal antibody, once generated, can be used in a variety of immunoassays which would be inherently useful for not only

research but as diagnostic tools" (see Wabl Declaration, page 1, second paragraph) is inconsistent with the teachings of Seaver. First, utility for further research is not a patentable utility. Brenner, Comr. Pats. v. Manson, 148 USPQ 689, (USSC 1966). The remaining asserted utility stated by Wabl, as "diagnostic tools," is at odds with the teachings of Seaver and Appellant has not provided any convincing objective evidence that the claimed antibodies overcome the problems taught by Seaver and, thus, would reasonably be expected to be useful as "diagnostic tools." Indeed, as evidenced by Seaver, in August 1994, one of ordinary skill in the art would not reasonably conclude that any monoclonal antibody would be obviously useful as a "diagnostic tool." To the contrary, one of ordinary skill in the art would reasonably conclude that the monoclonal antibody, more likely than not, would not be useful as a "diagnostic tool" absent convincing objective evidence of such use.

Further, Appellant cannot rely upon an asserted in vivo use for anti-TNF antibodies based on Wherry et al. as argued (see Brief, page 6, first full paragraph). Again, as with the asserted diagnostic uses, the evidence contradicts Appellant's asserted use as an in vivo therapeutic. Rhein (S2) teaches that clinical trials with various anti-TNF agents including monoclonal antibodies have failed. *Inter alia*, Rhein teaches that "Without a public announcement, Centocor halted preliminary Phase II trials in 61 patients of its anti-TNF monoclonal antibody, CenTNF, 'about a year ago'...Although Centocor is still studying the results from that trial, Dorgan said 'we knew from the data we knew, we didn't want to go forward with it" (see paragraph bridging pages 1 and 3). The teachings of Rhein are further confirmed by the evidence of Natanson et al. (T3). This reference is a review of treatment strategies and clinical trials for Septic Shock, a result of TNF overproduction in response to infection. Natanson et al. indicates that "Both

anti-interleukin-1 and anti-tumor necrosis factor (TNF) therapies have been beneficial in some animal models of sepsis but did not clearly improve survival in initial human trials, **and one anti-TNF therapy actually produced harm**" (see Abstract, emphasis added). Natanson et al. further describes in depth the results of clinical trials with anti-TNF antibodies (see page 775, last paragraph-page 776, column 1, last paragraph) and concludes by stating that "Anti-TNF and anti-IL-1 agents have not been shown to improve outcome in the treatment of human sepsis and septic shock and may, in fact, be potentially harmful" (see page 776, column 2, second full paragraph).

Thus, the evidence of Seaver contradicts Appellant's asserted diagnostic uses and the evidence of Rhein and Natanson et al. contradicts Appellant's assertion of therapeutic use. Therefore, one of ordinary skill in the art would not be able to use the claimed human monoclonal antibodies as a diagnostic or therapeutic agent with a reasonable expectation of success and without undue experimentation.

Further, in the instant application, it is not even clear that Appellant's antibodies would be suitable for immunoaffinity purification of TNF. Appellant's exemplar, the B5 human monoclonal antibody is characterized as being of such low affinity that affinity determination was not possible with conventional methods (see specification, page 17, first full paragraph). Indeed, detectable binding of soluble TNF by Mab B5 required a 300 fold higher concentration than did a similar murine monoclonal antibody, A10G10. It is well known in the art that monoclonal antibodies suitable for use as immunoaffinity purification reagents must have particular ranges of affinity for antigen. Hill (U3) teaches that "If the association constant for antibody and antigen is too high, it may be difficult to recover the antigen from the antibody. However, if

the association constant is too low, antigen may not bind efficiently to the immobilized antibody. An association constant of 10^4 to 10^8 is considered ideal..." (see page 124, first full paragraph). Thus, if the antibody affinity is too high, elution of the antigen will require such harsh conditions that the antigen is often denatured if it is released at all. If the affinity is to low, than the antigen-antibody interaction may lack specificity for the antigen and/or the antibody will not be able to bind antigen tightly enough to allow binding and washing of the affinity column prior to elution. Thus, even with affinity chromatography, the use of monoclonal antibodies is not a trivial matter.

Lastly, Appellant has taught that the B5 antibody is not neutralizing for TNF (see specification, page 18, line 8). This would also suggest that the claimed monoclonal antibody would not be useful as a therapeutic reagent since the antibody does not appear to exert any biologically/pharmaceutically significant effect on bound TNFα.

Thus, the evidence of record does not appear to teach one of ordinary skill in the art how to use the claimed monoclonal antibodies, either directly stated or obvious and readily apparent from the specification, without undue experimentation. The specification does not set forth a disclosed use for the claimed invention, and the evidence of record establishes that a patentable use would not be obvious to one skilled in the art. It is not clear that the claimed monoclonal antibodies can be used for purification, diagnostics, neutralization or therapy. Thus, in view of the evidence of record and in the absence of convincing evidence to the contrary, one of ordinary skill in the art would not be able to use the monoclonal antibodies of the claimed invention with any reasonable expectation of success and without undue experimentation.

It is noted that the arguments set forth above have been mostly directed to Appellant's specifically disclosed exemplar, the B5 human monoclonal antibody, and that the asserted uses of Appellant's invention could be considered to apply somewhat more broadly to claims directed to any human monoclonal antibody to TNFα as set forth in claims 1-10 and 12-14. However, one of ordinary skill in the art at the time the claimed invention was made would not have reasonably concluded that human monoclonal antibodies to human TNFα could exist since, prior to Appellant disclosure, there was no evidence to conclude that humans necessarily produced lymphocytes capable of secreting antibodies specific for human TNFα. Such human lymphocytes would be a necessary and essential starting material to produce human monoclonal antibodies to human TNFα. Thus, as asserted by Appellants, their own exemplar, B5, becomes the first known human monoclonal antibody to human TNFα and necessarily becomes representative of the characteristics and properties of human monoclonal antibodies to human TNFα that can be relied upon to enable how to make and use the broadly claimed genus of human monoclonal antibodies to human TNFα.

Further, Appellant has failed to enable the scope of the claimed invention. Appellant has only taught the production and characterization of the B5 human monoclonal antibody to tumor necrosis factor α meeting the limitations of the claims. Appellant has not provided evidence of other human antibodies specific for TNF or, more particularly, of other human monoclonal antibodies having the properties of B5 such as binding to cell surface TNF and down-regulating TNF secretion. Appellant has disclosed the existence of other human monoclonal antibodies which immunologically bind to TNF but Appellant does not characterize these antibodies further and it is impossible to determine the specificity and characteristics of these other antibodies from the record. There is insufficient evidence of

record to establish that monoclonal antibodies other than B5 would have the characteristics of, for example: 1) being of the IgG isotype (see claim 3); 2) being suitable for intravenous administration (see claim 5 and discussion of therapeutic utility set forth above); 3) having cross-reactivity with mouse TNF (see claim 6); 4) having specificity for TNFα (see all claims); 5) binding to non-neutralizing epitopes of TNF (see claim 8); 6) binding to cell surface TNF (see claims 9 and 13); capable of inhibiting secretion of TNF (see claims 10 and 14); 7) having a titer comparable to three high affinity neutralizing mouse monoclonal antibodies (see claim 12). With respect to claim 12, Appellant fails to specify which three mouse antibodies or what the titer of the preparation actually is. Appellant has only characterized one human anti-human TNF monoclonal antibody, B5, and even it does not meet all of the claims. It is an IgM, not an IgG. Appellant's own third party declaration of Matthias Wabl actually supports this lack of enablement objection. Dr. Wabl avers that "one skilled in the art, given the disclosure of the Patent Application **and** a related publication, Cellular Immunology, 152, 569-581 (1993),...could duplicate the Applicants' work and generate other cell lines that express human monoclonal antibodies that bind specifically to TNFα without undue experimentation using known screening techniques" (see Wabl, page 2, Paragraph #3 entitled "ENABLEMENT", emphasis added). However, the Cellular Immunology reference referred to by Dr. Wabl and apparently considered by him to be necessary for enablement, was published in December, 1993, 9 months after the filing date of the instant application. Therefore, the Cellular Immunology reference cannot be relied upon by Appellant for purposes of enabling the claimed invention.

As stated in the previous Office Actions, it is well known in the art that the production of monoclonal antibodies is

unpredictable and that there is a low probability of obtaining the same or similar monoclonal antibodies to a particular antigen. This low probability, together with the characteristics of the B5 human monoclonal antibody discussed above, would not allow one skilled in the art to produce the monoclonal antibodies of the claimed invention or similar antibodies without undue experimentation. This is particularly true where, as here, the invention is directed to human monoclonal antibodies, since human monoclonal antibodies necessarily require human lymphocytes producing the specific antibody.

Production of human monoclonal antibodies is fundamentally different from the production of murine monoclonal antibodies. In laboratory animals, one of ordinary skill in the art can immunize the animals by a variety of protocols designed to elicit particular isotypes or affinities. Such protocols are not readily available to the practitioner in the human monoclonal antibody art. Ethical restrictions preclude immunization and splenectomy of humans for monoclonal antibody production, methods commonly used in the well known murine monoclonal antibody art. Consequently, the person of ordinary skill in the art must necessarily rely on the ability to detect the existence of lymphocytes in human patients producing antibodies having the desired properties and to obtain such lymphocytes in a suitable manner and number for human monoclonal antibody production. To some extent, this limitation relies on providence for obtaining desired antibodies. This is particularly so when one is desiring to produce a human monoclonal antibody to a human protein which would normally be expected to be recognized as self and thus not elicit an immune response.

In the instant application, this lack of enablement for

human monoclonal antibody production is compounded by the fact that Appellant required a CMV positive donor (see page 11, lines 4-14) and that "it is unclear whether or not the CMV seropositive donor origin of B5 mAb is significant" (see page 37, lines 6-7). Thus, it is not clear from the teachings of the specification that one of ordinary skill in the art could obtain additional peripheral blood anti-human TNFα lymphocytes necessary for human hybridoma production, or even what criteria would be significant for identifying potential lymphocyte donors having anti-TNF human antibodies. Appellant argues that "the Examiner mistakenly believed that all of the antibodies listed in Table 1 of the Specific Embodiments originated from one donor" and cites the declaration of Dr. Gayle D. Wetzel, an Inventor of the subject matter of the instant application. Appellant further argues that "The Examiner also mistakenly believed that none of the other antibodies exhibit the same cell binding attributes as B5" (see Brief, page 7, first paragraph). Appellant further argues that "the Applicants did not find other 'B5-type' antibodies because, as is usual in the art, they used a preliminary screening assay to find an antibody that had the desired characteristics and from then on only that antibody was characterized. The antibodies that did not perform as well as B5 in the initial assay were not selected for further study" (see Brief, page 7, second full paragraph). Appellant further argues that "the enclosed declaration #1 by Dr. Wetzel clarifies the issue in that a CMV+ donor is probably not required and in any event, would not be hard to find" (see Brief, paragraph bridging pages 7-8). Appellant further argues that the declaration of Wetzel establishes that "making monoclonal antibodies is not unpredictable" (see Brief, page 8, first full paragraph), citing the decision of the Court in In re Wands, 8 USPQ2d 1400 (CAFC 1988). Finally, Appellant concludes that "to reproduce the instant invention, there are no special requirements of the donors which might make them hard to find.

The only experimentation that must be done to make human mAbs against TNFα is screening of hybridomas, which according to Wands is not considered undue experimentation" (see Brief, page 9, first full paragraph). These arguments are not persuasive.

First, it must be remembered that the claimed antibodies are **human monoclonal antibodies** directed to **human TNFα**, i.e, human antibodies to a human protein which the dogma of self v. non-self recognition of the immune system suggests should have been recognized as self. Thus, the existence of lymphocytes capable of responding to TNF by producing human antibodies strongly suggests that these are autoantibodies to human TNF (huTNFα). Thus, absent evidence to the contrary, one of ordinary skill in the art would reasonably conclude that donors producing anti-self antibodies (autoantibodies) specific for the donor's own TNF would (and should) be difficult to find.

Further, Appellant has not set forth convincing objective evidence to establish that the donors would not necessarily be CMV seropositive. Appellant has only set forth assertions by the Inventor unsubstantiated by factual evidence. As Appellant has stated, three of the five donors' CMV status is unknown and no conclusions can be drawn from this information. Further, the specification suggests that a CMV donor is needed, (see page 11, line 6) and Appellant clearly admits that the relevance of CMV seropositivity is unknown. Therefore, absent convincing evidence to the contrary, one skilled in the art would conclude from the specification that CMV seropositivity is at least desirable if not required.

Further, Appellant has not set forth any factual evidence to establish the reproducibility of the claimed monoclonal antibodies. Indeed, Appellant's own arguments indicate that the B5 antibody is the "best" antibody and even the H5 and 7T1

antibodies only "share **some** of the attributes of B5" (see Brief, page 7, first full paragraph, emphasis added). Thus, the only claim that could reasonably be considered to be enabled is claim 11 specific for the deposited B5 antibody. And again, as stated above, Appellant has even failed to teach one skilled in the art how to use the B5 antibody.

Therefore, in view of the above arguments, none of the claims can properly be considered to be enabled. Appellant has not provided any convincing factual objective evidence to support the scope of the remaining claims. As stated previously, and conceded by Appellant, the reproducibility of monoclonal antibodies is indeed unpredictable, and where, as here, the monoclonal antibodies are human monoclonal antibodies to a normal human protein, TNF, having the characteristics set forth in Appellant's claims, that unpredictability is greatly increased. For these reasons, and in view of the absence of convincing objective evidence to the contrary, the objection to the specification is deemed proper.

Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

(10) New Ground of Rejection.

This Examiner's Answer contains the following NEW GROUND OF REJECTION:

The objection to the specification and rejection of claims 1-14 under 35 U.S.C. § 112, first paragraph, for failing to provide an enabling disclosure set forth above is considered to be a **NEW GROUND** of rejection in view of the introduction of the evidence of Seaver (R3), Rhein (S3), Natanson et al. (T3) and Hill (U3) references relied upon in rebuttal of Appellant's

arguments and the declaration of Wabl.

(11) Response to Argument.

Appellant's arguments have been addressed above in the discussion of the Grounds of Rejection.

(12) Period of Response to New Ground of Rejection.

In view of the new ground of rejection, appellant is given a period of TWO MONTHS from the mailing date of this Examiner's Answer within which to file a reply to any new ground of rejection. Such reply may include any amendment or material appropriate to the new ground of rejection. Prosecution otherwise remains closed. Failure to respond to the new ground of rejection will result in dismissal of the appeal of the claims so rejected.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Robert D. Budens
Primary Examiner
Art Unit 1806

March 3, 1995

James A. Giblin
Miles Inc.
Fourth & Parker Streets
Berkeley, CA 94701
(510) 420-5511

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
4/5/95